Update on Anabolic Therapy

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Disclosures

Amgen: *Advising, Collaboration, Speaking*
Radius: *Advising, Collaboration, Speaking, Research Grant and Research Medication*
Obseva: *Consulting*
Enterabio: *Consulting*
Pfizer/Myovant: *Consulting*

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Very High Risk Patients: AACE Criteria

- AACE recommends considering abaloparatide, romosozumab, and teriparatide as initial therapy for very high-risk patients[1]
  - recent incident fracture (including subclinical vertebral fractures)
    - Also at high imminent risk (>10% over next 2 years)[2]
  - history of multiple fractures
    - Also at high imminent risk
  - fractures on approved osteoporosis medications or on medications known to cause skeletal harm
  - T-scores below −3.0
  - high falling risk or history of injurious falls
  - very high fracture probability (e.g. FRAX >30% MOF, >4.5% hip fx)

1. Camacho PM et al. Endocrine Practice 2020. AACE/ACE Guidelines 2020 Update.
2. Ferrari S et al. Swiss Med Wkly. 2020;150:w20352

3

Treatment for Very High Risk Patients

- Treatment goals for very high risk women, especially with high imminent risk:
  - Reduce fracture risk rapidly and potently
  - Sustain fracture risk reductions over time
  - Increase BMD rapidly and potently
- What are the data that illustrate the efficacy and safety of the anabolic agents (teriparatide, abaloparatide and romosozumab) in accomplishing these treatment goals?

Camacho PM et al. Endocrine Practice 2020. AACE/ACE Guidelines 2020 Update
Cosman F. Endo Practice 2020; 26:777-786

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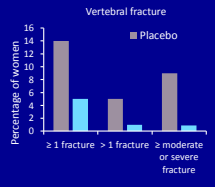
Teriparatide Pivotal Fracture Trial
Vertebral Fracture Risk Over 19 Months



Neer RM et al. N Engl J Med 2001;344:1434-41.

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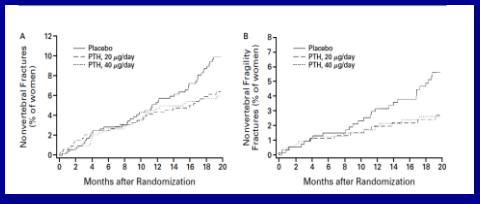
Teriparatide Pivotal Fracture Trial: Time to first Nonvertebral Fracture

All Nonvertebral Fractures | "Fragility" Nonvertebral Fractures



Neer RM et al. N Engl J Med 2001;344:1434-41

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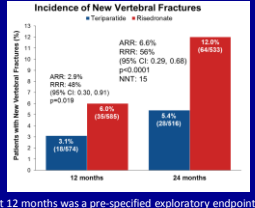
VERO: Teriparatide vs Risedronate in Patients with Prevalent Vertebral Fracture



N=1360 patients with prevalent vertebral fracture

Analysis at 12 months was a pre-specified exploratory endpoint. ARR, absolute risk reduction; RRR, relative risk reduction; CI, confidence interval; NNT, number needed to treat

Kendler DL et al. Lancet 2018;391:230-40

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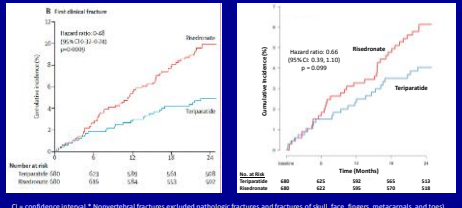
VERO: Teriparatide vs Risedronate
Time to First Clinical and Nonvertebral Fracture



CI = confidence interval. * Nonvertebral fractures excluded pathologic fractures and fractures of skull, face, fingers, metacarpals, and toes).

Kendler DL et al. Lancet 2018;391:230-40

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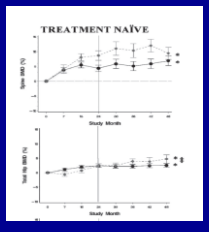
4 Year BMD Effects of Teriparatide (2 Years) Followed by Alendronate (2 Years) in Previously Untreated Women



Dotted line: Daily teriparatide for 2 years followed by alendronate for 2 years
Mean Spine BMD Gain:
With 4 year teriparatide/alendronate sequence: 9.4%

Mean Total Hip BMD Gain:
With 4 year teriparatide/alendronate sequence: 4.7%

Solid Line: Cyclic Treatment (3 months on/3 months off)- No significant improvement vs Standard Regimen

Cosman F et al JCEM 2015; 100:2769-2776
Cosman F et al Bone 2019; 120:246-253

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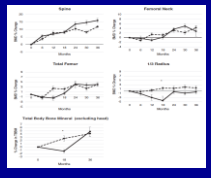
Sequential Teriparatide and Denosumab: Cyclic vs Standard Regimen

- N=70 women with osteoporosis randomized to:
  - Standard: TPTD 18 months followed by Dmab 18 months
  - Cyclic: Cycles of TPTD for 6 months followed by Dmab 6 months- total of 3



36 Month BMD Changes

	Standard	Cyclic
LS:	16%	12%
TH:	4%	4%
FN:	3%	4%
Rad:	-0.4%	+1.5%
TB:	4.8%	4.1%

Cosman F et al JBMR 2020; 35:219-225

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Beyond Osteoporosis: Teriparatide and Lumbar Spine Fusion

- Meta-analysis of 12 studies (only 3 RCTs) with total of 771 patients
  - 377 treated with teriparatide but duration and timing re surgery highly variable
  - Controls included both placebo and bisphosphonate-treated
- Results:
  - Lumbar spine fusion rates about 2-fold higher in teriparatide-treated vs non-teriparatide treated patients ($p<0.00001$)
  - Also significant reduction in subsequent vertebral fractures (84%), late sagittal malalignment, and pain

Fatima N et al. Neurosurg Rev (2021) 44:1357–1370

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Beyond Osteoporosis: Teriparatide and Fracture Healing

- Systematic Review of 11 RCT studies with total of 1452 patients, 91% women (n=1333); mean age 72
  - Control groups could be placebo, positive comparator (bisphosphonate) or standard care
  - All fracture sites included (vertebrae n=789, hip n=343, radius n=102, humerus n=40, tibia n=13, atypical femur n=13)
- Results:
  - No difference in rate of healed fracture at first reported time point
  - Overall teriparatide improved functional outcomes and reduced pain with teriparatide

Eastman K et al. Ost Int 2021;32:1531-1546

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Teriparatide vs Placebo on Pelvic Fracture Healing

- RCT of women and men (total N=33) within 1 month of acute pelvic fracture randomized to teriparatide vs placebo for 3 months
- Fracture healing assessed at 3 months by CT
- Pain and Physical Function also assessed (by Short Physical Performance Battery including 4 m walking speed, repeated chair stands, and balance) and Timed Up and Go test
- Results:
  - no group differences in fracture healing (by CT) or pain
  - significant improvement in two measures of physical performance with TPTD compared to placebo group (group difference p=0.03)

Nieves JW, Cosman F, et al Ost Int 2022; 33:239–250

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Teriparatide: Long-term Post-marketing Surveillance Study for Osteosarcoma

- 3808 incident osteosarcoma cases identified in adults 40+ in 30 participating cancer registries from 1/2003-12/2016
  - 24% of adult osteosarcoma cases (n= 1173) completed phone interview where risk factors ascertained, including exposure to teriparatide
    - mean age 61, equal female/male, 19% RT, 4% Paget's, 4% FH
    - 3 patients had exposure to teriparatide before osteosarcoma dx
- Over same time period, there were 5,432,764 teriparatide person-yrs
  - With known background incidence of 2.5 per million
    - expected number of cases in teriparatide users was 4.17
  - reported standardized incidence ratio was 0.72 (90%CI, 0.20-1.86)
- Conclusion: No association of teriparatide exposure with osteosarcoma

Gilsenan A et al. JBMR 2021; 36:244-251

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Teriparatide Registry: Linkage to Osteosarcoma Risk

- Patients who received a teriparatide prescription over 10 years were matched to unexposed patients in 2 different cohorts
  - Matched for osteoporosis
  - Matched with the general population who received a different prescription
- Osteosarcoma diagnoses obtained through linkage to state cancer registries
- Total of 18 osteosarcoma cases were identified
  - 3 in the teriparatide users
  - 6 in the matched osteoporosis cohort
  - 9 in the general population cohort
- Conclusion: Incidence Rate Ratios no higher than expected for background incidence

Kellier-Steele N et al. Bone 2022; https://doi.org/10.1016/j.bone.2022.116394

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Label Changes for Teriparatide and Abaloparatide

- In November 2020, the FDA approved label changes for teriparatide
  - removed the 2-year lifetime treatment limitation
  - removed boxed warning about the potential risk of osteosarcoma.
- FDA approved the removal of the boxed warning regarding potential risk of osteosarcoma from the abaloparatide (TYMLOS) label on December 22, 2021

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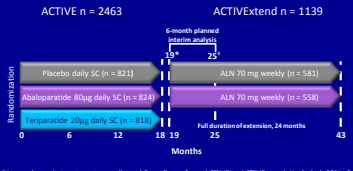
Pivotal Abaloparatide Trial: ACTIVE and ACTIVExtend



*1-month gap in treatment was allowed for rollover from ACTIVE to ACTIVExtend. Included 92% of eligible patients
†Investigators and patients remained blinded to original treatment assignment for 6 months of the extension.

Bone et al. JCEM 2018;103:2949-57

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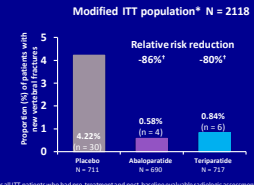
ACTIVE: New Vertebral Fractures with Abaloparatide and Teriparatide over 18 Months



*Includes all ITT patients who had pre-treatment and post-baseline evaluable radiologic assessments; †P< 0.001 vs placebo.

Miller PD et al. JAMA 2016;316:722-33

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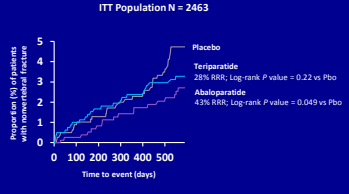
ACTIVE: Time to First Nonvertebral Fracture



Miller PD et al. JAMA 2016;316:722-33

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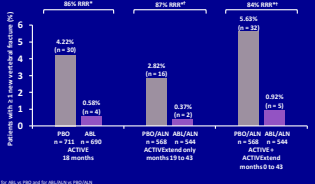
ACTIVE and ACTIVExtend: New Vertebral Fractures



*P < 0.001 for ABL vs PBO and for ABL/ALN vs PBO/ALN
† No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo; **RRR**, relative risk reduction

Bone et al. JCEM 2018;103:2949-57

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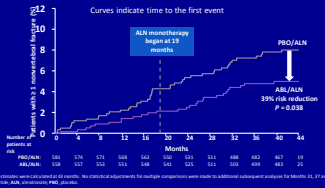
ACTIVE and ACTIVExtend: Time to First Nonvertebral Fx



Kaplan-Meier estimates were calculated at 43 months. No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37 and 43.
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

Bone et al. JCEM 2018;103:2949-57

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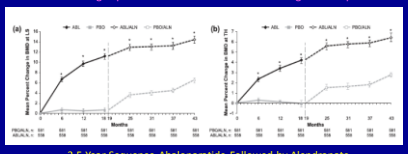
BMD Gains with Abaloparatide (18 Months) Followed by Alendronate (2 Years) in ACTIVE/ACTIVExtend

Mean % Change Spine BMD | Mean % Change Total Hip BMD



3.5 Year Sequence Abaloparatide Followed by Alendronate

Mean Spine increase 14.4% | Mean Hip BMD increase: 6.4%

Bone et al. JCEM 2018;103:2949-57

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Consistency of Fracture and BMD Effects of Abaloparatide

- In ACTIVE predefined subgroup analyses, BMD and fracture reduction effects were very similar across age range, BMD levels, and prevalent vertebral or prior clinical fracture, with no significant subgroup/treatment interactions[1]
- Similar BMD gains in
  - the very old (n= 94 women ≥age 80)[2]
  - the young (n=296 women 49-64 years old)[3]
  - women with DM (n=198)[4]
  - women with CKD[5]
    - n=1276 with GFR 60-89 ml/min
    - n=527 with GFR 37-60 ml/min

1. Cosman F et al JBMR 2017
2. McClung M et al Menopause 2018
3. Saag K et al Clin Therap 2021
4. Dhaliwal et al JBMR Plus 2020
5. Bilezikian JP et al CMRO 2019

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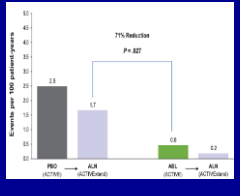
PostHoc Comparisons of Abaloparatide vs Alendronate from ACTIVE and ACTIVExtend

- Fracture rates with 18 months of abaloparatide compared to fracture rates
  - with 18 months of placebo during ACTIVE
  - with 24 months of alendronate during ACTIVE Extension
- New vertebral fractures were lower with abaloparatide vs alendronate (p<0.03)
- Trend toward reduced nonvertebral fracture with abaloparatide versus alendronate (reduced by 45%; *P* = .11)

New Vertebral Fracture Rate



Leder BZ et al JCEM 2020; 105: 938–943

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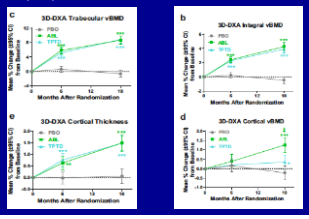
Abaloparatide: 3D Hip Modeling

- Subgroups of 250 women from each arm of ACTIVE with available DXA hip BMD
  - 3D-Modeling using Hip Shaper Software to estimate compartmental volume (trabecular and cortical) of the hip
  - Analyses performed blinded to treatment arm



- Both ABL and TPTD increased integral and trabecular volumetric BMD and cortical thickness
- Only ABL increased cortical vBMD c/w less intracortical remodeling with ABL vs TPTD

Winzenrieth R OI 2021; 32:575-583

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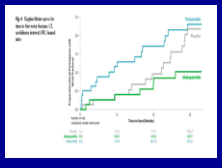
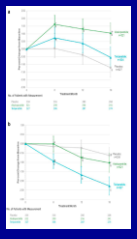
ACTIVE Trial: Effects on Wrist Fracture and Wrist BMD

Time to first wrist fracture



ABL vs TPTD, HR 0.43, p=0.052
ABL vs PBO, HR 0.49, p=0.11



Ultradistal Radius BMD

1/3 Radius BMD

Watts NB et al. Ost Int 2019; 30:1187–1194

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Cardiovascular Safety: Abaloparatide and Teriparatide

- Cardiovascular safety profile from ACTIVE trial
- Mean pulse increase at 1 hour post dose
  - 8 beats/min with abaloparatide
  - 5 beats/min with teriparatide
  - 1 beat/min with placebo
    - Changes resolved within 4 hours
- Mean BP change 1 hour post dose (systolic/diastolic)
  - -2.7/-3.6 mm Hg with abaloparatide
  - -2.0/-3.6 mm Hg with teriparatide
  - -1.5/-2.3 mm Hg with placebo

Cosman F et al JCEM 2020; 105:3384-3395

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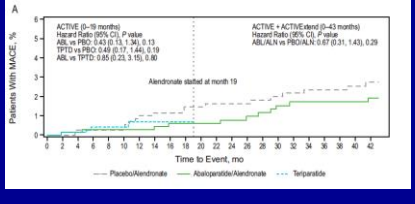
Time to First MACE (Major Adverse Cardiac Event) in ACTIVE and ACTIVExtend



Cosman F et al JCEM 2020; 105:3384-3395

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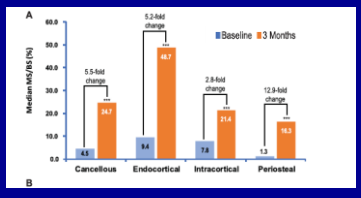
Abaloparatide Effect on Bone Formation at 3 Months

23 women had baseline tetracycline label prior to treatment and a second tetracycline label after 3 months of abaloparatide, followed by iliac crest biopsy



Dempster DW et al. JBMR 2021; 36:644-653

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WearABLe: Transdermal vs Subcutaneous Abaloparatide Administration

- About 500 women with osteoporosis randomized to transdermal 300mcg vs subcutaneous abaloparatide 80mcg for 1 year
- Primary Endpoint: Lumbar spine BMD
  - increase with transdermal 7.1% (CI 6.2, 8.0)
  - Increase with subcutaneous 10.9% (CI 9.9, 11.8)
  - Rx difference of 3.7% was greater than noninferiority margin set at ≤2%
- Secondary Endpoint: Total Hip BMD
  - increase with transdermal 2.0%
  - increase with subcutaneous 3.7%

Radius Press Release Dec 8, 2021

Radius Press Release Dec 8, 2021. Radius Announces Results from the wearABLe Trial

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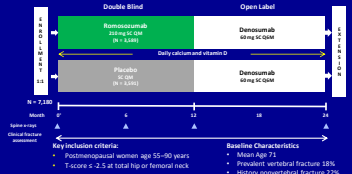
FRAME Study Design: Romosozumab vs Placebo Followed by Denosumab



Cosman F, et al. *N Engl J Med* 2016;375:1532-1543

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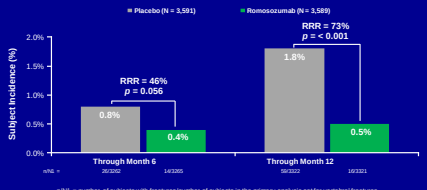
FRAME: New Vertebral Fracture Incidence Through Month 12 (Coprimary Endpoint)



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures
p-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture

Cosman F et al. N Engl J Med 2016;375:1532–43.

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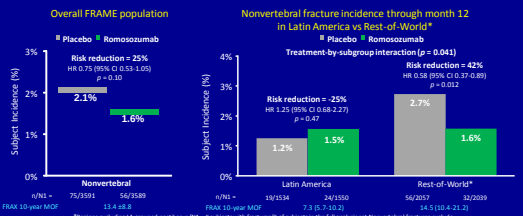
FRAME: Nonvertebral Fracture Outcome Through Month 12



*Regions excluding LA grouped post hoc. n/N1 = # subjects with fractures/# of subjects in the full analysis set.Nonvertebral fractures exclude skull, face, metacarpals, fingers, and toes, pathologic fractures and those due to high trauma. CI, confidence interval; HR, hazard ratio.

Cosman F, et al. *N Engl J Med* 2016; 375:1532-1543 and Cosman F, et al. *J Bone Miner Res* 2018; 33:1219-1226.

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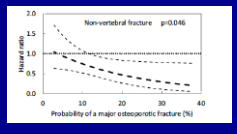
FRAME: Baseline Fracture Probability and Effect of Romosozumab vs Placebo on Nonvertebral Fracture



Romosozumab has a greater effect against NVF in higher risk patients.

Effect of Romosozumb vs Placebo on Nonvertebral Fracture: HR with 95% CI by Baseline FRAX Probability for Major Osteoporotic Fracture

McCloskey EV Ost Int 2021; 32:1601-1608

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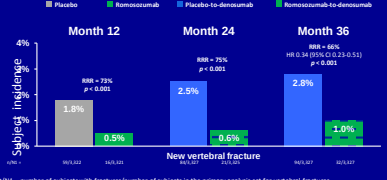
FRAME Extension: New Vertebral Fracture Incidence Through Month 36



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures. *P*-values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure based on odds ratio. *P*-value for month 36 is nominal, based on odds ratio. Data displayed for 12-month and 24-month periods are as reported for the primary analysis. CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction.

Lewiecki EM, et al. *J Bone Miner Res* 2019;34:419-428.

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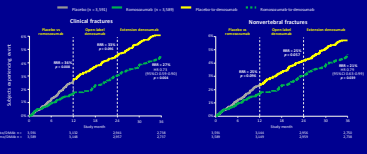
FRAME Extension: Time to First Clinical and Nonvertebral Fracture Through Month 36



Nonvertebral fractures comprised the majority (more than 80%) of clinical fractures. n = number of subjects at risk for event at time point of interest. Relative risk reduction and p-value for 12-month and 24-month periods are adjusted values based on a sequential testing procedure as reported for the primary analysis. *P*-values for month 36are nominal. CI, confidence interval; DMAb, denosumab; HR, hazard ratio; Pbo, placebo; Romo, romosozumab; RRR, relative risk reduction.

Lewiecki EM, et al. *J Bone Miner Res* 2019;34:419-428.

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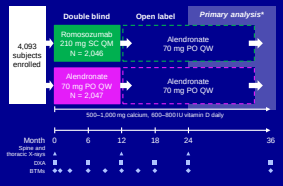
ARCH Study Design: Romosozumab Versus Alendronate Followed by Alendronate

Active-Cont**R**olled Fra**C**ture Study in Postmenopausal Women at **H**igh Risk of Fracture



*Median time on study at primary analysis was 33 months (IQR 27–40).
BTM, biochemical marker of bone turnover; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; IQR, interquartile range; PM, postmenopausal; PO, oral; QW, weekly; TH, total hip.

Key inclusion criteria:

- PM women aged 55–90 years
- T-score TH or FN ≤ –2.5 and ≥ 1 moderate or severe vertebral fracture or two mild vertebral fractures
- T-score TH or FN ≤ –2.0 and ≥ 2 moderate or severe vertebral fractures or recent hip fracture

Baseline characteristics:

- Mean age: 74 years
- Mean T-score spine: –3.0
- Mean T-score total hip: –2.8
- Vertebral fracture: 96%
- Recent hip facture: 9%
- History of nonvertebral fracture: 38%

Saag K, et al. *N Engl J Med.* 2017;377:1417–27.

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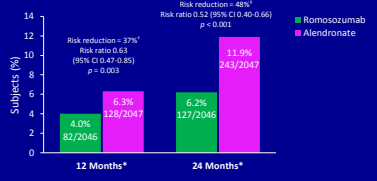
ARCH: Incidence of New Vertebral Fracture Through Month 24 (Primary Endpoint)



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.
*Missing fracture status was imputed by multiple imputation for patients without an observed fracture at an earlier time point.
n and % based on the average across 5 imputed data sets. †Risk reduction at 12 months by LOCF: 36% (nominal p = 0.008) romosozumab 3.2% (55/1,696) vs alendronate 5.0% (85/1,703). ‡Risk reduction at 24 months by LOCF: 50% (nominal p < 0.001) romosozumab-to-alendronate 4.1% (74/1821) vs alendronate-to-alendronate 8.0% (147/1840).
CI, confidence interval; LOCF, last observation carried forward.

Saag K, et al. *N Engl J Med* 2017;377:1417-1427.

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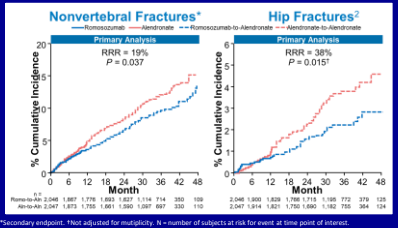
ARCH: Incidence of Nonvertebral and Hip Fracture at Primary Analysis



*Secondary endpoint. †Not adjusted for multiplicity. N = number of subjects at risk for event at time point of interest.

Saag K et al. N Engl J Med 2017;377:1417-27.

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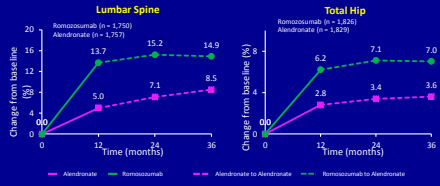
3 Year BMD Gains with Romosozumab for 12 Months Followed by Alendronate for 2 Years (ARCH)



Saag K, et al. *N Engl J Med.* 2017;377:1417–27.

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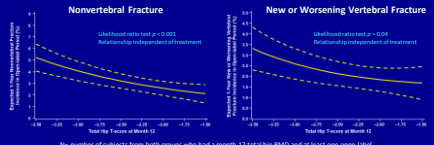
ARCH Study: Total Hip T-score at Month 12 and Subsequent Risk of Fracture



N= number of subjects from both groups who had a month 12 total hip BMD and at least one open-label alendronate dose (total N = 3,342; romosozumab n = 1,679; alendronate n = 1,663). Dashed lines are upper and lower 95% confidence limits. Analysis for nonvertebral fracture based on the Cox proportional hazards model with time to fracture as the response and total hip T-score at 12 months as covariate. For vertebral fracture, analysis based on logistic regression model. *P* values based on the likelihood ratio test.

Cosman F, *et al. JBMR* 2020; 35: pp 1333–1342.

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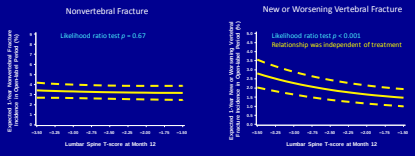
ARCH Study: Lumbar Spine T-score at Month 12 and Subsequent Fracture Incidence



N = number of subjects who had a month 12 lumbar spine BMD and at least one open-label alendronate dose. Romosozumab , n = 1625, Alendronate, n = 1607. Dashed lines are upper and lower 95% confidence intervals. Analysis based on the Cox proportional hazards model with time to fracture as the response and lumbar spine T-score at month 12 as a covariate. For vertebral fracture, analysis based on logistic regression model P-values based on the likelihood ratio test.

Cosman F, *et al. JBMR* 2020; 35: pp 1333–1342.

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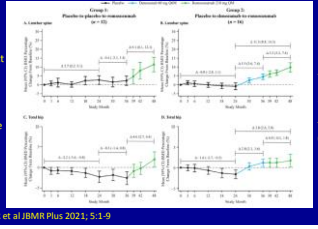
Romosozumab after 1 year Denosumab Phase 2 Study Extension

- N=12 randomized to receive Pbo for 3 years followed by Romo (left)
- N=16 randomized to receive Pbo for 2 years, Dmab 1 year and then Romo (right)

Romo Effect After Pbo: LS increase 9.1%

TH increase 4.6%



Romo Effect After Dmab: LS increase 5.3%

TH increase 0.9%

McClung MR et al JBMR Plus 2021; 5:1-9

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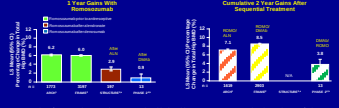
Importance of Treatment Sequence with Romosozumab: Total Hip BMD



n = number of patients who received romosozumab and had total hip BMD measurements at baseline and at specified timepoints. *Patients had received oral bisphosphonate for ≥ 3 years before screening and alendronate (70 mg QW) for ≥ 1 year immediately before screening. BMD was not measured in the 1 year of alendronate before romosozumab. †Patients received placebo during Months 0–24, denosumab during Months 24–36, and romosozumab during Months 36–48; cumulative gains are relative to the Month 24 baseline. ALN = alendronate; DMAb = denosumab; LS = least squares; N/A = not applicable; ROMO = romosozumab.

[1] Saag KG, et al. *N Engl J Med*. 2017;377:1417-1427.
[2] Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.
[3] Langdahl BL, et al. *Lancet*. 2017;390:1585-1594.
[4] McClung MR, et al. JBMR Plus 2021; 5:1-9
[5] Cosman F et al, Osteoporosis Int 2022

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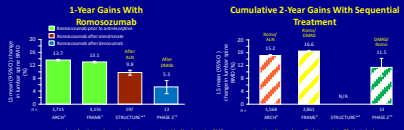
Importance of Treatment Sequence With Romosozumab: Spine BMD



n = number of patients who received romosozumab and had lumbar spine BMD measurements at baseline and specified time points. *Patients had received oral bisphosphonate for ≥ 3 years before screening and alendronate (70 mg QW) for ≥ 1 year immediately before screening. BMD was not measured in the 1 year of receiving alendronate before romosozumab. †Patients received placebo during months 0–24, denosumab during months 24–36, and romosozumab during months 36–48; cumulative gains are relative to the month 24 baseline.

[1] Saag KG, et al. *N Engl J Med*. 2017;377:1417-1427.
[2] Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.
[3] Langdahl BL, et al. *Lancet*. 2017;390:1585-1594.
[4] McClung MR, et al. JBMR Plus 2021; 5:1-9
[5] Cosman F et al, Osteoporosis Int 2022

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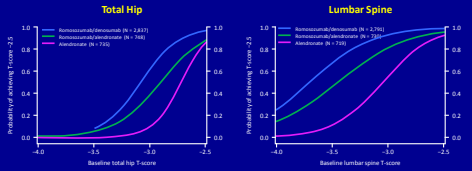
Probability of Achieving T-Score > –2.5 in 3 Years with ALN, Romo/ALN, or Romo/Dmab by Baseline BMD



With T-Scores below -2.75 in TH and below -3.0 in LS, low probability of achieving T-Score >-2.5 with 3 years of alendronate.

Cosman F, et al. *JBMR Plus*. 2021;doi:10.1002/jbm4.10546.

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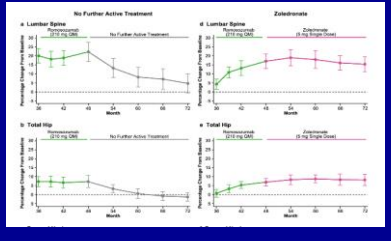
BMD Maintenance after Romozumab with Zoledronic Acid



McClung MR, et al OI 2020; 31:2231–2241

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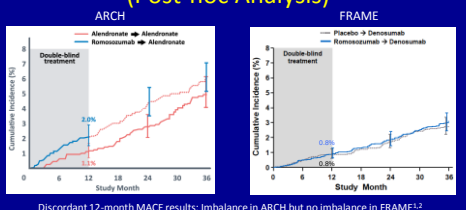
Time to First Positively Adjudicated MACE (Post-hoc Analysis)



Discordant 12-month MACE results: Imbalance in ARCH but no imbalance in FRAME[1,2]

EVENITY® (romosozumab) Approved Product Information. Available at: www.amgen.com.au/Evenity-PI
Amgen Briefing Information for the January 16, 2019 Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee. Available at: https://www.fda.gov/media/121255/download. Accessed 26 March 2020.

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Perspective on CV Events with Romosozumab

- MACE rates for alendronate-treated women were reduced for only the first 3 months
  - Events occurred in parallel in the two groups subsequently.
  - Although some data suggest alendronate might reduce CVD, it would not occur so rapidly or last for such a brief period.
- The estimated reduction in MACE for alendronate vs romosozumab is outside the confidence intervals for previous trials.
- There was no change in MACE rate at 12 months when alendronate started and romosozumab discontinued.
- The difference in *all serious* cardiac AEs (including heart failure) was not significant between romosozumab and alendronate groups.
- There was no difference between romosozumab and placebo groups in the larger FRAME study.

Conclusion: The CV signal is probably *not related* to romosozumab and is likely due to chance.

Cummings SR and McCulloch C OI 2020; 31:1019-1021

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Cardiovascular and Cerebrovascular Safety in Japan

Table 1
Cardiovascular safety of romosozumab report compared to Shiga Cohort Study in Japan.

	Stroke	ICD
Romosozumab [18]	0.164	0.1007
Shiga Cohort [19,20]	0.40	0.17

Incidence with 100 person-years reported on reference numbers of 18, 19, and 20.
ICD, ischemic cardiovascular diseases.

Yasuhiro Takeuchi. Osteoporosis and Sarcopenia 7 (2021) 89e91

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Summary

- Optimal treatment of very high risk patients is with anabolic therapy first followed by a potent antiresorptive agent
- All anabolic agents stimulate bone formation and new bone growth but the mechanism of action differs
- As initial therapy, anabolic medications reduce vertebral and nonvertebral fractures compared with both placebo and bisphosphonate treatments
- Treatment sequence matters
  - BMD attained on or after therapy is a predictor of subsequent fracture risk
  - BMD gain is greatest when anabolic agents are given first with most important differential effect in the total hip

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